Chocolate and cardiovascular disease: a sweet deal?

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Online publish-ahead-of-print 20 February 2012

This editorial has been guest edited by Prof. Stefano Taddei, Università degli Studi di Pisa, Italy.

This editorial refers to ‘Cardiovascular effects of flavanol-rich chocolate in patients with heart failure’, by A.J. Flammer et al., on page 2172

‘Take two of these chocolates daily, and call me in a month.’ Who among us would not want to be able to provide such a delicious prescription to our patients who carry the complicated and eventually fatal diagnosis of heart failure? Unfortunately, the solution is not that simple, yet the recent study by Flammer et al. may bring us a step closer to understanding the relationship between cocoa, endothelial function, and cardiovascular health.

Flammer et al. present a largely positive, double-blind, randomized controlled trial (RCT) comparing the effect of commercially available flavanol-rich chocolate (FRC) vs. control chocolate (CC) on endothelial function, an indicator of increased morbidity and mortality, in patients with moderate (New York Heart Association class ≥ II) heart failure. The authors found significant short-term (2 h) and longer term (4 weeks) improvement in flow-mediated dilation (FMD), their primary endpoint, of the brachial artery after consumption of FRC vs. CC. Importantly, these calorically neutral supplements had no effect on the patients’ body weight or fasting glucose measurements. Other pertinent findings in the study include mostly comparable secondary endpoints in these groups, such as blood pressure, body weight, lipid fractions (with the exception of HDL-cholesterol), inflammatory markers, antioxidants, baroreceptor function, and long-term platelet adhesion, underscoring the complex relationship between traditional risk factors and vascular function. On the other hand, blood pressure tended to decrease in the FRC group, consistent with previous observational studies and RCTs; however, the current study may have been underpowered to detect such differences in a small sample size. Finally, while not quite statistically significant, there was a strong trend toward endothelial-independent vasoconstriction after 4 weeks of FRC consumption, which was not detected at 2 h after FRC treatment or at any time point after CC consumption. While this was not elaborated upon, further elucidation of the underlying mechanisms might help expound upon the implications of the results. Further investigation regarding cocoa and alternative regulatory factors such as endothelin-1, angiotensin II, thromboxanes, endothelial-derived hyperpolarizing factor (EDHF), prostaglandins other than 8-isoprostane, or other vasoactive cytokines, and their effect on cardiovascular disease (CVD) parameters affecting those with heart failure could be undertaken as a follow-up study.

Additional noteworthy findings regarding secondary endpoints included a reduction in platelet adhesion seen 2 h after FRC administration, and, interestingly, unaltered insulin sensitivity among those consuming FRC for 4 weeks compared with those randomized to CC, who had a significant decrease in insulin sensitivity. As longer term FMD assessments were performed after an extended fast, the authors point out that the sustained improvement in endothelial function at 4 weeks with a non-sustained amelioration in platelet function indicates that the extended ingestion of cocoa could lead to phenotypic changes in the endothelium conferring an enduring therapeutic benefit in this population of sick patients. Thus, the proposed mechanism ascribing cocoa with enduring alterations in nitric oxide (NO) bioavailability is certainly plausible, and should prompt further investigation regarding the effect of nutraceuticals on the mechanisms causing heart failure and monitoring such effects via endothelial function.

Although few, this study did have some limitations, including small sample size, the inability to control completely the remainder of the subjects’ diet, adherence to study substance, and medications taken by the patients which might mitigate any ill effects or bioavailability of the FRC. Clearly, the authors took measures to reduce the impact of these factors, and the improvements in endothelial function are of such magnitude that sample size was not an issue. Additionally, the authors carefully documented flavanol...
concentration before and after the administration of FRC to show significant increases in plasma levels. They also took great effort to ensure a weight- and calorie-neutral study, avoiding confounders typically seen in dietary RCTs. Despite the absence of direct measurements of NO or its bioavailability, it is not unlikely that the effect may be mediated by tilting the balance in favour of the endothelial-dependent vasodilators as opposed to the vasoconstrictors such as endothelin-1 and angiotensin II.

The interest in cocoa as a cardiovascular nutraceutical initially arose after the Kuna Indians, native inhabitants of islands off the coast of Panama, were found to have a low prevalence of hypertension even among the elderly, despite daily consumption of immense amounts of (often salt-enriched) cocoa—a substance that until that point was thought to only be deleterious to one’s health. Since then, large-scale observational studies have documented the improvement in blood pressure as well as CVD mortality in subjects who regularly consume cocoa. Other epidemiological studies have shown that cocoa flavanoids might reduce myocardial infarction, stroke incidence, as well as CVD mortality. Meta-analyses evaluating the effect of cocoa consumption on CVD have also demonstrated a reduction in CVD mortality and blood pressure as well as an improvement in lipid profiles and FMD, presumably through anti-inflammatory mechanisms and augmented platelet function. Smaller RCTs have shown cocoa products to be associated with reduced systolic and diastolic blood pressures, decreased LDL oxidation, and improved endothelial function, presumably due to the high polyphenol content of cocoa. These results could not be duplicated with similar doses of milk, white, or semi-sweet chocolate. Complicating the issue, however, is the considerable variability in the concentrations of cocoa in various compounds, leading to divergent results of ostensibly RCTs. The typical cocoa concentration of commercially available dark chocolate in Europe is nearly 35–50%, while in US dark chocolate the cocoa concentration tends to be closer to 15%. An important strength of the study of Flammer et al. is that the authors utilized a standardized commercially available substance containing 70% cocoa, and confirmed polyphenol concentrations in both the FRC and patients’ serum. Polyphenols have been shown to exert beneficial effects through an increase in the bioavailability of NO, as well as antioxidant, anti-inflammatory, and antiplatelet effects, presumably leading to improved endothelial function, reduced blood pressure, and improved insulin resistance. Indeed, cocoa is one of the few nutraceutical agents included in both the European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines as being able to provide protection against CVD-causing atherosclerosis.

The benefits conferred by chocolate were examined in the study of Flammer et al. by its effects on endothelial function. The earliest injury imposed by cardiovascular risk factors is often at the interface between the vascular wall and the circulation, involving initial damage of the endothelial surface. The presence of endothelial dysfunction serves as an independent marker for the progression...
of CVD and subsequent cardiovascular events. Endothelial dysfunction has been associated with reduced NO bioavailability, inability to relieve oxidative stress, and an increased inflammatory state in CVD, and has been found to be prevalent in patients with heart failure (Figure 1). What is more, endothelial dysfunction is associated with increased mortality in patients with heart failure. Multiple efforts through RCTs have been made to ameliorate the symptoms and causative mechanisms of heart failure, including omega-3 fatty acids, antioxidant vitamins (such as C and E), and even cardiac resynchronization therapy. All of which led to improvements in surrogate markers for heart failure and, most importantly, endothelial function. While initially debated, microvascular endothelial dysfunction has been demonstrated in heart failure both with and without preserved ejection fraction, closely correlating with exercise capacity. Endothelial function has been shown to improve with multiple treatment modalities in a wide variety of heart failure patients, reflecting the notion that there are multiple origins to heart failure. The results gleaned from this trial and other preceding studies appear to illustrate multiple ways that endothelial function can be improved in those with heart failure (Figure 1), and diverse promising modalities available to treat heart failure (medications, nutraceuticals, procedures, etc.). It would appear that in patients with heart failure, frequent monitoring of the earliest damaged and repaired organ (the endothelium) could serve as an important clinical tool for physicians. Furthermore, the results of the study of Flammer et al. offer a specific mechanistic explanation for a potentially underutilized and possibly cost-effective therapy—cocoa—in the treatment of heart failure. Likewise, there is a potential to use endothelial function not only as an initial staging diagnostic modality for heart failure, but also to monitor medication compliance and individualize treatment strategies (Figure 1). Well-established links between endothelial function and exercise performance among those with heart failure with preserved ejection fraction imply that linking symptomatic, functional improvement to expected improvements in endothelial function in heart failure patients is an area ripe for study. This highly effective, inexpensive, and reproducible technique can easily be applied to the patient population with heart failure, which tends to be at higher risk for adverse cardiovascular events and death, and requires frequent changes to therapy. Multiple efforts through RCTs have been made to improve with multiple treatment modalities in a wide variety of heart failure patients, reflecting the notion that there are multiple origins to heart failure. The results gleaned from this trial and other preceding studies appear to illustrate multiple ways that endothelial function can be improved in those with heart failure (Figure 1), and diverse promising modalities available to treat heart failure (medications, nutraceuticals, procedures, etc.).

Conflict of interest: none declared.

References